



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

JUL 19 1995

OFFICE OF  
PREVENTION, PESTICIDES  
AND  
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Consideration of Unconditional Registration for the New Biochemical, Clarified Hydrophobic Extract of Neem Oil (PC Code 025007) - DECISION MEMORANDUM

FROM: Janet L. Andersen, Acting Director  
Biopesticides and Pollution Prevention Division *Janet L. Andersen*

TO: Daniel M. Barolo, Director  
Office of Pesticide Programs

ISSUE

Should the Agency grant an **unconditional registration under FIFRA § 3(c)(5)(c)** to the subject product which contains the new active ingredient, **Clarified Hydrophobic Extract of Neem Oil (PC Code 025007)**.

I. **RECOMMENDATIONS / DATA GAPS / EXECUTIVE SUMMARY**

A. **RECOMMENDATIONS**

Data requirements for granting this registration under Section 3(c)(5) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) have been met. The data have been reviewed and Biopesticides and Pollution Prevention Division foresees no unreasonable adverse effects from the use of this product and recommends unconditional registration.

B. **DATA GAPS**

There are 2 data gaps. However, exposure to aquatic species is not expected when the Clarified Hydrophobic Extract of Neem Oil (025007) [CHEx Neem Oil (025007)] is used according to labeling instructions. Therefore, for the purpose of this regulatory action, these data are not required.

C. **EXECUTIVE SUMMARY**

The new active ingredient, CHEx Neem Oil (025007), consists of oils (100± 3% glycerides and fatty acids) which are present in the daily diet, are GRAS (21 CFR 172.860) and have low toxicity in mammalian (Toxicology Categories III and IV) and avian studies. CHEx Neem Oil (025007) is the manufacturing product for fungicides with a non-toxic mode of action, such as NeemGuard™ (11688-O) Botanical Insecticide / Fungicide for control of black spot, rusts and powdery mildew on non-food/non-feed ornamentals, trees and shrubs. In general, microorganisms in the soil and aquatic environments readily utilize these oily substances as a source of energy. All data



source of energy. All data requirements have been fulfilled for the new active ingredient, CHEx Neem Oil (025007), with the exception of aquatic toxicity studies, Guidelines 154-8, Freshwater Fish LC<sub>50</sub> and 154-9, Freshwater Invertebrate, LC<sub>50</sub>. However, with precautionary labeling for the proposed uses (terrestrial, non-food/non-feed, ornamental), these data are not necessary for making a risk assessment and a finding of no unreasonable adverse effects.

**D. OFFICE DIRECTOR'S CONCURRENCE**

Biopesticides and Pollution Prevention Division recommends that Clarified Hydrophobic Extract of Neem Oil (PC Code 025007) be unconditionally registered under 3(c)(5) of FIFRA.

Concurrence: 

Non Concurrence: \_\_\_\_\_

Date: \_\_\_\_\_

JUL 19 1995



**CLARIFIED HYDROPHOBIC EXTRACT of NEEM OIL [CHEx Neem Oil (025007)]**  
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## II. OVERVIEW

### A. BIOCHEMICAL OVERVIEW

Neem oil (= extract, PC Code 025006), a hydrophobic (lipophilic) extract from the seeds of the neem tree, *Azadirachta indica* L., is classified as a biochemical active ingredient with anti-fungal activity and a non-toxic mode of action. When applied to plant leaves, neem oil acts as a protectant and fungistat by interfering with the attachment of fungal spores to the leaf. Applications of neem oil to leaves are ineffective only 24 hours after fungal spores have infected the leaves. Furthermore, fungal spores dipped in neem oil do not sporulate; however, when the spores are washed in water to remove the neem oil extract, the spores germinate. Similar studies with rose leaves infected with black spot show that neem oil reduces the rate of infection, fungal growth, and sporulation, but does not actually kill the fungus.

Clarified Hydrophobic Extract of Neem Oil (CHEX Neem Oil, 025007)<sup>1</sup> is the technical grade manufacturing product consisting primarily of glycerides and fatty acids (100±3%) which are constituents of the human diet and are Generally Recognized As Safe (GRAS<sup>2</sup>). Other components of neem oil (025006), if at all present, exist as impurities at trace levels (<0.02-0.04%).

### B. USE PROFILE

CHEX Neem Oil (025007) will be used in end-product formulations, such as **NeemGuard™ (11688-O)** Botanical Insecticide/Fungicide for non-food/non-feed crops. As a fungicide, NeemGuard™ (11688-O) will be used for management of black spot, rusts, and powdery mildew on bedding plants, ornamentals, trees, and shrubs, in and around greenhouses, commercial nurseries, and homes. As an insecticide, NeemGuard™ will be used to control to control flies, thrips, mealy bugs, leafminers, loopers, caterpillars, army worms, aphids, psyllids, fruit flies, beetles, mites, scales, midges and grasshoppers on ornamentals, trees and shrubs, in and around greenhouses, commercial nurseries, and other commercial and residential structures.

### C. REGULATORY HISTORY

On December 31, 1992, W.R. Grace & Co. - Conn. (GRACE) applied for registration of CHEX Neem Oil (025007) [= Neem Oil TGAI (11688-I)] and NeemGuard™ (11699-O) Botanical Insecticide/Fungicide. CHEX Neem Oil is a new active ingredient and NeemGuard™ is a formulated product containing 90% Neem Oil TGAI and 10% inerts.

On May 12, 1994, GRACE was notified that ... "Given the requested information on the non-toxic mode of action of neem oil, the Science Analysis Branch / Health Effects Branch has recommended to the Office of Pesticide Programs (OPP) Biotechnology Workgroup that neem oil consisting predominantly (>99%) of free fatty acids and glycerides, be classified as a biochemical pesticide when used as a fungicide. ..." This ruling focused narrowly on the non-toxic mode of action on the target pest (fungal spores) and the use of CHEX Neem Oil as a fungicide.

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<sup>1</sup> CHEX neem oil, clarified hydrophobic extract of neem oil, here-to-fore, has been called Neem Oil TGAI and other terms in various submissions. This abbreviation and terminology is introduced in order clarify ambiguities and avoid confusion with names that have various meanings and appear in the open literature and in submissions to EPA / OPP.

<sup>2</sup> Long chain fatty acids are considered GRAS for use in foods under 21 CFR 172.860 Fatty acids; 172.862 Oleic acid derived from tall oil fatty acids; and §184.1065, linoleic acid; §184.1323, glyceryl monooleate; §184.1324, glyceryl monostearate; and §184.1505 mono- and diglycerides.



The Agency determined that CHEx Neem Oil<sup>3</sup> (025007) meets the criteria for a select category of pesticide active ingredients (biopesticides) for which a reduced set of generic data requirements are appropriate for registration. (Refer to 40 CFR 158.690 *Biochemical pesticides data requirements*.)

On April 12, 1995, a notice was published in the **Federal Register [60 FR 18599]** of Applications to Register Pesticide Products Not Included In Any Previously Registered Products by W.R. Grace & Co.-Conn., including:

File Symbol: **11688-I.** Product name: **Neem Oil TGAI.** Biochemical.  
Active Ingredient: Neem Oil 100 per cent.  
Proposed Classification/Use: General. For manufacturing use only for formulation of insecticides.

File Symbol: **11688-O.** Product name: **NeemGuard Botanical Fungicide.** Biochemical.  
Active Ingredient: Neem Oil TGAI at 90% per cent.  
Proposed Classification/Use: General. For effective management of black spot, rusts, and powdery mildew on bedding plants, ornamentals, trees, and shrubs, in and around greenhouses, commercial nurseries, and homes.

File Symbol: **11688-RI.** Product name: **NeemGard Botanical Insecticide.** Biochemical.  
Active Ingredient: Neem Oil TGAI at 90% per cent.  
Proposed Classification/Use: None. For use to control a variety of foliar plant diseases including rots, mildews, rusts, leaf spots, scab, and blights. Kills/repels insect pests such as whiteflies, aphids, scales, mealybugs, and mites.

No comments have been received by the Agency in response to the **Federal Register Notice, Environmental Protection Agency OPP-30385, FRL-4945-5.**

Since the filing of the Federal Register Notice, (1) a label was submitted that includes the manufacturing product used for end-use formulations of fungicides and insecticides for non-food/non-feed use and (2) BPPD has suggested that the active ingredient be identified as Clarified Hydrophobic Extract of Neem Oil, PC Code 025007 (CHEx Neem Oil, 025007) to distinguish this a.i. from neem oil (025006) and other products which have hydrophilic neem substances as the active ingredient.

NeemGuard (11688-O) is a formulated end-use product for non-food/non-feed use that is the subject of a separate registration action that will follow shortly after this registration action.

NeemGard (11688-RI) is a formulated end-use product for food/feed use that is the subject of a separate registration action that requires the issuance of a tolerance or an exemption from the requirement of a tolerance for 9 crop groups, ~249 crops and ~117 pests.

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<sup>3</sup> neem oil (= neem extract, PC Code 025006) - an oil expressed from the seed-kernels of the Indian neem tree (*Azadirachta indica* L.) consisting of glycerides (mono-, di-, and tri-) and limonoids, including azadirachtin, nimbin, nimbiol, q.q.v., salannin; about 2% bitters [See Appendix 1: Glossary of Products Derived from the Neem Tree]



### III. SCIENCE ASSESSMENT

#### A. Physical and Chemical Properties Assessment

**Product Chemistry Assessment**      **CHEX Neem Oil (025007)**      **Acceptable**

Under CFR §158.690 and, in accordance with Subdivision M §151-10 to §151-13 and §151-15 to §151-17, product chemistry data are required for biochemical pesticides. The Registrant submitted these data for (1) CHEX Neem Oil (025007) and (2) NeemGuard™ (11688-O), End-Use Product, 90% CHEX Neem Oil (025007) and 10% inerts). All Guideline Requirements have been satisfied.

Neem oil (= extract, PC Code 025006), extracted from seeds of the neem tree, *Azadiracta indica* L., consists of glycerides (mono-, di- and tri-), fatty acids and limonoids including azadirachtin, nimbin, nimbiol, salannin and bitters (compounds containing organic sulfur). **CHEX Neem Oil (025007)**, prepared from neem oil (025006) by proprietary processes, is the technical grade manufacturing that consists of glycerides and fatty acids (100±3%) that are constituents of the human diet and are Generally Recognized As Safe (GRAS<sup>4</sup>). Other components of neem oil (025006), if, at all present in CHEX Neem Oil (025007), exist as impurities at trace levels (<0.02-0.04%).

Guideline	Title	MRID No.	Status
151-17	Physical and Chemical Properties	426124-01 433610-01 GRACE Letter 8.29.94	Acceptable Acceptable Acceptable

Guideline	Characteristics	CHEX Neem Oil (025007)	NeemGuard™ (11688-O)
63-2	Color	Brown	Brown
63-3	Physical State	Liquid	Liquid
63-4	Odor	peanuts, garlic	peanuts, garlic
63-5	Melting Point	Liquid at 20°C	NR
63-6	Boiling Point (760 mm Hg)	>300°C	NR
63-7	Density	0.9052	0.9137
63-8	Water Solubility (g/100ml)	<0.002 g/g @ 21°C	NR
63-9	Vapor Pressure	<1.33 x 10 <sup>-5</sup> pascal (1 x 10 <sup>-7</sup> torr)	
63-10	Dissociation Constant	Non-ionic Does Not Dissociate	NR
63-11	Octanol/Water Par- tition Coefficient	Nonpolar Organic Not Miscible in Water	NR
63-12	pH	Not Miscible in Water Does Not Dissociate	
63-13	Stability	Stable*	NR
63-15	Flammability [Flame Blown Out by Oil Vapor at >200°C]	No Flash at 200°C;	
63-16	Explosibility	No Exotherms Observed	No Exotherms Observed
63-17	Storage Stability	NR	NR
63-18	Viscosity	47.1 cP	53.9 cP
63-19	Miscibility	Not Miscible in Water	
63-20	Corrosion Characteristics	None	None

\* Actual stability not provided      NR = Not Required

<sup>4</sup> Long chain fatty acids are considered GRAS for use in foods under 21 CFR 172.860 Fatty acids; 172.862 Oleic acid derived from tall oil fatty acids; and §184.1065, linoleic acid; §184.1323, glyceryl monooleate; §184.1324, glyceryl monostearate; and §184.1505 mono- and diglycerides.



Guideline	Title	MRID No.	Status
151-10	Identity of the Active Ingredient	426124-01 GRACE Letter 8.29.94	Acceptable Acceptable

**3.B.1. CHEx Neem Oil (025007) (Manufacturing Product)**

Identification of CHEx Neem Oil (025007) is summarized below:

Chemical Name	Neem Oil (= neem extract)	CHEx Neem Oil (025007)
PC Code	025006	025007
CAS Registry No.	8002-65-1	None Assigned
Common Name	neem oil; margosa oil; nim oil	CHEx Neem Oil (025007)
Molecular Formula	Not Applicable	Not Applicable
Source	Neem Tree, <i>Azadiracta indica</i>	Neem Tree, <i>Azadiracta indica</i>
Mode of Action		Fungicidal (fungistat) (Non-Specific Mode of Action)

151-12	Formation of Unintentional Ingredients	MRID No. 426124-01	Acceptable
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CHEx neem oil (26007) contains free fatty acids and glycerides. There are no concerns for the formation of unintentional ingredients that are of potential toxic nature (such as aflatoxins) during the manufacturing process because of precautionary storage conditions.

[ See CBI Appendix ]

151-13	Analysis of Samples	MRID No. 426124-01	Acceptable
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Both, raw neem oil (= neem extract, 025006) and CHEx neem oil (025007), consist primarily of glycerides and smaller amounts of free fatty acids.

[ See CBI Appendix ]

151-15	Certification of Limits	MRID No. 426124-01	Acceptable
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Analytical data for samples from 5 batches of CHEx Neem Oil (025007) (PC Code 025007) have been submitted to the Agency.

[ See CBI Appendix ]

151-16	Analytical Methods	MRID No. 426124-01 Letter 8.29.94	Acceptable Acceptable
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The Registrant submitted published methodologies for the preparation of methyl esters of long-chain fatty acids and analysis of triglycerides and fatty acids gas chromatography.

**151-17 Physical and Chemical Properties**

151-17 (63-8)	Solubility	Letter 8.29.94	Acceptable
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The solubility in water is <0.002 g/g at 21°C.



The vapor pressure of constituent glycerides of CHEX Neem Oil (025007) was determined to be  $<1.33 \times 10^{-5}$  pascal ( $1 \times 10^{-7}$  torr) with a gas saturation procedure. The data are acceptable.

GRACE requested and received a waiver from the requirement to generate data for the Octanol/Water Partition Coefficient because of the low solubility of CHEX Neem Oil (025007).



## B. Human Risk Assessment

CHEX Neem Oil (025007), free of foreign materials (i.e., lipophilic microbial contaminants, aflatoxins), is composed of long chain fatty acids (free and as glycerides) which are present in the normal diet (~90 grams of lipid in the daily diet) and are Generally Recognized As Safe (GRAS<sup>5</sup>). After the removal of hydrophilic lipids and organic-S compounds by the manufacturing process, the composition is similar to that of other plant oils which are used as food items.

### 1. Hazard Assessment - Acute Toxicity

The acute mammalian toxicity studies for **CHEX Neem Oil (025007)** were limited to the acute dermal toxicity test (152-11, MRID 426124-02); a full complement of acute toxicology studies was not considered essential because data were available for NeemGuard™ (11688-O).

With a small complement of studies for CHEX Neem Oil (025007) [Product Chemistry, Acute Dermal Toxicity, Genotoxicity], the toxicology data for NeemGuard™ is bridged to complete the database for CHEX Neem Oil (025007). This is possible because the 10% inerts of NeemGuard™ is not expected to confound the toxicity testing of the CHEX Neem Oil (025007). In view of the GRAS nature of the components of CHEX Neem Oil (025007) and the low toxicity in Tier I acute studies using CHEX Neem Oil (025007) in the formulated end-use product, higher tier toxicology studies are not needed for making risk assessments. (HED Memorandum, 7.22.94)

The Science Analysis Branch / Health Effects Division summarized the study results in the following table.

**Toxicology Database for CHEX Neem Oil (025007) and NeemGuard™ (11688-O)**

Guideline	Title	Organism	Test Material	Results	Toxicology Category	MRID #
152-10	Acute Oral Toxicity	Rat	NeemGuard™	LD <sub>50</sub> > 5 g/kg	IV	42612502
152-11	Acute Dermal Toxicity	Rabbit	NeemGuard™	LD <sub>50</sub> > 2 g/kg	III	42612503
			CHEX Neem Oil	LD <sub>50</sub> > 2 g/kg	III	42612402
152-12	Acute Inhalation	Rat	NeemGuard™	LD <sub>50</sub> > 5 g/kg	IV	42612504
152-13	Primary Eye Irritation	Rabbit	NeemGuard™	Minimal Irritant <sup>6</sup>	III	42612505
152-14	Dermal Irritation	Rabbit	NeemGuard™	Minimal Irritant <sup>7</sup>	IV	42612506
152-15	Hypersensitivity	Guinea Pig	NeemGuard™	Minimal <sup>8</sup> Sensitization	N/A	42612507
152-17	Genotoxicity Studies	Salmonella	CHEX Neem Oil	No Detectable Mutations		43361002

<sup>5</sup> Long chain fatty acids are considered GRAS for use in foods under 21 CFR 172.860 Fatty acids; 172.862 Oleic acid derived from tall oil fatty acids; and §184.1065, linoleic acid; §184.1323, glyceryl monooleate; §184.1324, glyceryl monostearate; and §184.1505 mono- and diglycerides.

<sup>6</sup> Slight conjunctival irritation (hyperemia, chemosis, discharge) in 6/6 rabbits, cleared by 48 h in 1 rabbit, 72 h in the other 5.

<sup>7</sup> Barely perceptible to well-defined erythema at all test sites up to 24 hours; at 48 hours, erythema perceptible at only 3 sites; cleared by 72 hours

<sup>8</sup> Faint, non-confluent erythema at 3 test sites 24 hours post-challenge; at 48 hours, only 1 site exhibited faint, non-confluent erythema. Upon rechallenge 5 days later, very faint erythema (confluent to non-confluent) observed at 6 test sites at 24 hours post-challenge, and 5 sites at 48 hours



The toxicology data set for CHEx Neem Oil (025007) is complete when the acceptable data for NeemGuard™ (11688-O) are used. The following data are required under 40 CFR § 158 Subpart D, in accordance with Subdivision M §152-10 to §152-23 of the Pesticide Assessment Guidelines:

**Toxicology Database for CHEx Neem Oil (025007) (PC Code 025007)**

Guideline	Title	Organism	CHEx Neem Oil PC Code 025007	NeemGuard™ 11688-O
152-10	Acute Oral Toxicity	Rat	Bridged	426125-02
152-11	Acute Dermal Toxicity	Rabbit	426124-02	426125-03
152-12	Acute Inhalation	Rat	Bridged	426125-04
152-13	Primary Eye Irritation	Rabbit	Bridged	426125-05
152-14	Primary Dermal Irritation	Rabbit	Bridged	426125-06
152-15	Hypersensitivity Study	Guinea Pig	Bridged	426125-07
152-17	Genotoxicity Detection	<i>Salmonella</i>	Reverse Mutation <sup>9</sup>	433610-02
152-18	Immune Response	GRACE Letter	12.09.94	Waiver Granted <sup>10</sup>
152-20	90-Day Feeding (1 spp.)	GRACE Letter	12.09.94	Waiver Granted <sup>11</sup>
152-21	90-Day Dermal (1 spp.)	GRACE Letter	12.09.94	Waiver Granted <sup>10</sup>
152-22	90-Day Inhalation (1 spp.)	GRACE Letter	12.09.94	Waiver Granted <sup>10</sup>
152-23	Teratogenicity (1 spp.)	GRACE Letter	12.09.94	Waiver Granted <sup>10</sup>

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<sup>9</sup> 152-17 Genotoxicity (*Salmonella*) MRID 433100-02  
Genotoxicity studies are required for food/feed uses, but not required for this registration which deals with non-food/non-feed uses. [Although a waiver from the requirement for the generation of data for the 152-17 Genotoxicity Studies would be supported (Agency Letter of July 29, 1994), a *Salmonella* / microsome reverse mutation study had already been submitted and reviewed.]

<sup>10</sup> The proposed use patterns and protective clothing is not likely to increase exposure to that which already exists via the diet (SAB/HED Memo 7.22.94).

<sup>11</sup> The Neem Oil TGA1 consists primarily of long chain fatty acids and glycerides that are naturally found in foods and are generally recognized as safe (GRAS) when used as additives to foods under 21 CFR 172.860 and 172.862, and are exempt from tolerance when used in accordance with good agricultural practice (40 CFR 180.1001). (SAB/HED Memo 7.22.94).



***Salmonella* / Microsome Reverse Mutation**

Although a waiver from the requirement for the generation of data for the 152-17 Genotoxicity Studies would be supported (Agency Letter of July 29, 1994), a *Salmonella* / microsome reverse mutation study had already been submitted and was subsequently reviewed. This study is Acceptable and satisfies the guideline requirement for an end-use product for food/feed uses.

A *Salmonella* / Mammalian-Microsome Reverse Mutation Assay (Ames Test) with a Confirmatory Assay with levels of CHEx Neem Oil (025007) at 100-5000  $\mu\text{g}/\text{plate}$  is acceptable. CHEx Neem Oil (025007) does not increase the number of histidine revertants per plate in any of the 5 tester strains, either with or without microsomal enzymes (S9) prepared from Aroclor™-induced rat liver, in both initial and confirmatory *Salmonella*/mammalian-microsome reverse mutation assays with tester strains (TA98, TA100, TA1535, TA1537, TA1538 with additional mutations) at levels from 6.67 to 5000  $\mu\text{g}/\text{plate}$  with ethanol vehicle controls and positive mammalian enzyme controls [rat liver microsome (2-aminoanthracene) or no microsome control (2-nitrofluorene or sodium azide or ICR-191)].

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|----|--|-----------------------|
| 2. | <b>Dose Response Assessment</b>  | <b>Not Applicable</b> |
| 3. | <b>Dietary Exposure and Risk Characterization</b>                      | <b>Not Applicable</b> |
| 4. | <b>Occupational and Residential Exposure and Risk Characterization</b> |                       |

Labeling of Manufacturing Use Product with the signal word, "Caution", is satisfactory for CHEx Neem Oil (025007) and the end use product NeemGuard™ (11688-O).

For the end-use product, NeemGuard™ (11688-O), applied in a 1:128 dilution to non-crop ornamental plants from a 5-gallon backpack, the exposure to CHEx Neem Oil (025007) would be less than the equivalent of 0.01% of the lipid in the daily diet = a 10,000 fold dilution in the diet.

For the end-use product, NeemGuard™ (11688-O), applied at a 1:128 dilution (1 fl oz/gal) to non-agricultural crops from a 5-gallon back-pack with 25-40 psi pressure, a worker wearing personal protective equipment (short-sleeved shirt, long pants, shoes, socks and no gloves\*), would be exposed to ~<1 mg of CHEx Neem Oil (025007) which is ~0.011% of the uptake of lipids from the daily diet (90 g/70 kg man inhaling at a rate of 25 liters/minute). This calculation is prorated from a computation by PHED for the combined dermal and inhalation (total) exposure for 1 lb ai sprayed from a backpack scenario\* described above.

$$\begin{aligned} \text{CHEx Neem Oil (025007)} &= 0.9052 \text{ g ai/ml} & 1 \text{ fl oz} &= 29.6 \text{ ml} & 5 \text{ fl oz} &/ 5\text{-gal} \\ 0.9052 \text{ g ai/ml} \times 29.6 \text{ ml / fl oz} \times 5 \text{ fl oz / 5 gal} &= 133.97 \text{ g ai/ 5-gal} \end{aligned}$$

$$\begin{aligned} \text{PHED computes Total Exposure to 1 lb ai sprayed under above scenario*} &\rightarrow 16,309 \mu\text{g ai} \\ (26.79 \text{ g ai / fl oz} \times 5 \text{ fl oz}) / 453.6 \text{ g/lb} &= (x \mu\text{g ai}) / 16,309 \mu\text{g ai Total Exposure} \\ \text{Total Exposure:} &x \mu\text{g ai} = 4816 \\ (4816 \mu\text{g ai}) / 90 \text{ g lipid in daily diet} &= 5.35 \times 10^{-3} \% \text{ of the lipid in daily diet} \end{aligned}$$

According to label instructions, when NeemGuard™ is applied at a dilution of 1:128, workers may be exposed during a 5-gallon application to < 5,000  $\mu\text{g}$  of CHEx Neem Oil (025007); after 18 5-gallon applications, to Total Exposure would be <90,000  $\mu\text{g}$  (= <90 mg) of CHEx Neem Oil (025007), or < ~0.1% of the lipid in the daily diet. These calculations are very conservative because gloves and long-sleeve shirt were not included in the scenario. Moreover, toxicity testing does not indicate a level of concern from acute exposure to NeemGuard™ (11688-O). Home owners may be expected to be exposed less than professional workers.



**C. ENVIRONMENTAL ASSESSMENT      CHEx Neem Oil (025007)**

**1. Ecological Toxicity Data**

Under CFR §158.690 and, in accordance with Subdivision M §154-6 to §154-11, nontarget organism, fate and expression data requirements are required for biochemical pesticides. The Registrant submitted these data for the manufacturing use of CHEx Neem Oil (025007).

All Guideline Requirements for the end-use product, NeemGuard™ (11688-O) have been satisfied, with the exceptions of Guidelines 154-8 and 154-9. However, these studies on aquatic organisms are not essential if the risk assessment takes into account mitigating language on the label. In addition, the GRAS nature of CHEx Neem Oil (025007) and its potentially rapid utilization by ubiquitous microbes should obviate its accumulation in the environment.

Guideline	Title	Organism	MRID No. / Letter
154-6	Avian Acute Oral LD <sub>50</sub> 14-Day	bobwhite quail <i>Colinus virginianus</i>	426124-03 Practically Nontoxic (Core)
154-7	Avian Acute Dietary LC <sub>50</sub> 8-Day	bobwhite quail <i>Colinus virginianus</i>	426124-04 Core (Acceptable)
154-8	Freshwater Fish LC <sub>50</sub>	fathead minnow <i>Pimephales promelas</i>	436307-01 Invalid Precautionary Labeling Recommended
154-9	Freshwater Invertebrate LC <sub>50</sub>	daphnid <i>Daphnia magna</i>	436307-02 Invalid Precautionary Labeling Recommended
154-10	Nontarget Plant	Waiver	Letter 12.09.94
154-11	Nontarget Insect	Waiver	Letter 12.09.94 Precautionary Labeling Recommended

**D. ECOLOGICAL EFFECTS**

Guideline	Title	Organism	MRID No. / Letter
154-6	Avian Acute Oral LD <sub>50</sub> 14 day	Bobwhite Quail <i>Colinus virginianus</i>	426124-03 Practically Nontoxic (Core)

CHEx Neem Oil (025007) (purity of 98.962%), administered by way of gelatin capsule to bobwhite quail (*Colinus virginianus*), is practically nontoxic. Although a no-effect level could not be determined because of transient gastrointestinal effects shortly after dosing, the acute effect of CHEx Neem Oil (025007) appears to be minimal.

The LD<sub>50</sub> was >2,150 mg/kg CHEx Neem Oil (025007). A no-observed-effect-level (NOEL) could not be determined because of the chalky excreta in the lowest dose level during day 1.



154-7	Avian Acute Dietary LD <sub>50</sub> 8 day	Bobwhite Quail <i>Colinus virginianus</i>	426124-03 Core (Acceptable)
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CHEX Neem Oil (025007) (98.962% purity) is practically nontoxic to bobwhite quail (*Colinus virginianus*) when combined in the diet at levels of 312, 625, 1,250, 2,500 and 5,000 ppm.

No mortalities occurred in any of the groups and none of the birds exhibited adverse clinical signs during the 8-day study, although some minor effects showed up in the group receiving the highest concentration (5000 ppm).

154-8	Freshwater Fish LC <sub>50</sub>	Fathead Minnow <i>Pimephales promelas</i>	436307-01 Invalid Precautionary Labeling Recommended
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The freshwater fish LC<sub>50</sub> study with fathead minnows, *Pimephales promelas*, for determining the susceptibility of aquatic vertebrates to **CHEX Neem Oil (025007)** is invalid because (1) no distinction could be made at the lower dosage levels (2000 mg/L) between the measured amounts of Neem Oil in the control waters (0 mg/L) and the treatment waters (2000 mg/L)

initially and terminally. These variable measurements of Neem Oil initially and at the termination of the experiments confounded the results, and prevented clear interpretations of no observable effects level. The information is considered supplemental for determining a risk assessment.

The risk to nontarget aquatic organisms from inadvertent exposure should be mitigated through the appropriate language under the heading of ENVIRONMENTAL HAZARDS on the end-use product label which reads: "ENVIRONMENTAL HAZARDS / Do not apply directly to water, or to areas where surface water is present, or to intertidal areas below the mean high water mark. Do not contaminate water by cleaning or disposal of equipment washwaters." With these precautionary label statements, this study does not have to be repeated.

154-9	Freshwater Invertebrate LC <sub>50</sub>	daphnid <i>Daphnia magna</i>	436307-02 Invalid Precautionary Labeling Recommended
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The freshwater invertebrate study for determining the susceptibility of aquatic invertebrates to **CHEX Neem Oil (025007)** is invalid because of the variability in the measurements of Neem Oil in the control [(0 mg/L, nominal; 200 mg/L measured initially; 350, 620 mg/L measured terminally)] and the experimental exposures [(620, 290 mg/L, measured initially; 430, 350 mg/L measured terminally)]. The information is considered supplemental for determining a risk assessment.

With the precautionary label statements listed above (154-8), this study does not have to be repeated.

154-10	Nontarget Plant	MRID No. Letter	Waiver Granted	May 11, 1995
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The Registrant provided an adequate rationale to justify a waiver from the requirement to generate data in support the Guide Line # 154-10, *Non-Target Plant Testing, Tier I*, as recommended by a previous reviewer. Although **CHEX Neem Oil (025007)** is similar to oils in action and phytotoxicity, it is safe for use on most plants. However, slight phytotoxicity is seen on blooms of highly sensitive plants (petunias and impatiens) when applied at high ambient temperature (>90°F). Below 90°F, phytotoxic effects are negligible, even on highly sensitive plants.



GRACE proposes to register **NeemGuard™** (11688-O) as a product for nonfood use to control black spot, rusts, and powdery mildew on bedding plants, trees and shrubs in and around greenhouses, commercial nurseries and homes. [NeemGuard™ contains 90% CHEx Neem Oil (025007), a manufacturing product]. Instructions consistent with the proposed uses should be displayed on end-use product labels.

**154-11 Nontarget Insect**

**MRID No.**

**Letter**

**Waiver Granted**

**May 23, 1995**

**Waiver Granted**

**Precautionary Labeling Recommended**

The request of GRACE for a waiver from the requirement to generate data in support the Guideline No. 154-11, *Nontarget Insect Testing, Tier I*, as recommended by an EFED reviewer and concurred by BPPD reviewers, is generally supported by literature submitted by the Registrant that a wide range of insects is susceptible to neem oil (= neem extract). The proposed use of **NeemGuard™** (11688-O) is a product for ornamental (non-food/non-feed) use to control insects and mites on bedding plants, trees and shrubs in and around greenhouses, commercial nurseries and homes.

The rationale and supporting information provided justifies a waiver for the generation of data for nontarget insect requirements because the number of insects that have a susceptible stage of development to the non-toxic mode of action indicates that CHEx Neem Oil (025007) or **NeemGuard™** is a somewhat broad spectrum insecticide.

The following end-use product label Precautionary Statement must be placed on the label under the Environmental Hazards heading:

**BEE HAZARD**

This product is toxic to bees exposed to direct treatment. Do not apply this product while bees are actively visiting the treatment area.

Insects susceptible to CHEx Neem Oil (025007) (PC Code 025007) or **NeemGuard™** (11688-O) include:

mealybugs	leafminers	loopers	caterpillars
beet armyworms	hornworms	spruce budworms	webworms
hornworms	psyllids	aphids	pine sawflies
leaf hoppers	fruit flies	elm leaf beetles	tent caterpillars
bagworms	mites	scales	Japanese beetles
	midges	grasshoppers	

**E. ECOLOGICAL RISK ASSESSMENT**

**CHEx Neem Oil (025007)** presents a minimal risk to the environment with respect to persistence and exposure of most organisms because it lacks a toxic mode of action. The GRAS components of CHEx Neem Oil (025007) are ubiquitous at low levels in the environment and are readily utilized by plants and microbes. The greatest potential threats in the environment may occur if large quantities of Neem Oil inadvertently enter the aquatic ecosystem and interrupt life stages of organisms which have dependence on surface tension of the water for survival or the free exchange of gases across the air-water interface.

**F. ENDANGERED SPECIES CONSIDERATIONS**

**CHEx Neem Oil (025007)** presents a minimal risk to the environment with respect to persistence and exposure of most organisms because it lacks a toxic mode of action. The GRAS components of CHEx Neem Oil (025007) are ubiquitous at low levels in the environment and are readily utilized by plants and microbes. Furthermore, the use pattern of CHEx Neem



Oil (025007) is for manufacturing purposes and its uses are under contained conditions.

#### IV. RISK MANAGEMENT DECISION

Unacceptable adverse effects from the use of CHEX Neem Oil (PC Code 025007), a hydrophobic extract of seeds of the neem tree, *Azadirachta indica* L. are not expected. The active ingredient is composed of naturally occurring lipids which are common components of the normal diet and are considered to be GRAS. The components are ubiquitous in the environment and rapidly degraded by native populations of microorganisms. CHEX Neem Oil (025007) generally has no toxic mode of action when it is used for pesticidal purposes. There are no concerns for the formation of unintentional ingredients that are of potential toxic nature (such as aflatoxins) during the manufacturing process because of precautionary storage conditions. Industrial precautions should be employed during manufacturing because volatile and inflammable substances are used.

Data requirements for granting this registration under Section 3(c)(5) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) have been met. The data have been reviewed and Biopesticides and Pollution Prevention Division foresees no unreasonable adverse effects from the use of this product.



VI. Appendix A. GLOSSARY of Substances from the Neem Tree, *Azadirachta indica* L.

CHEX Neem Oil (025007) (PC Code 025007) is the new active ingredient, as defined in this glossary:

1. The New Active Ingredient

**CHEX Neem Oil (025007), Clarified Hydrophobic Extract of neem oil (PC Code 025007)**

A clarified hydrophobic (organic solvent) extraction product, consisting of glycerides (mono-, di-, and tri-) and fatty acids, obtained from neem oil (= neem extract, PC Code 025006) with further purification by proprietary processes. CHEX Neem Oil (025007) is a mixture of >99% free fatty acids and glycerides and <0.04% azadirachtin and <0.02% salannin.

**clarified neem oil**

A synonym for CHEX Neem Oil (PC Code 025007) - a clarified hydrophobic extract of neem oil (extract, 025006) which has undergone additional purification by a proprietary process. GRACE (151-13, MRID No. 426125-05)

2. **Synonymous Terms for neem oil (PC Code 025006) in the Scientific Literature and Submissions**

**neem oil (= neem extract, PC Code 025006, CAS No. 8002-65-1)**

An oil expressed from the seed-kernels of the Indian tree (*Azadirachta indica* L.) consisting mostly of glycerides (mono-, di- and tri-) and limonoids, including azadirachtin, nimbin, nimbiol, qqv., salannin; about 2% bitters (Merck Index 11: 6357).

**Neem oil (also referred to as lipophilic neem extract)**

"Neem oil (also referred to as lipophilic neem extract) is a botanical extract derived from seeds of the neem tree, *Azadirachta indica*. ..."

(Letter from GRACE to Agency, November 2, 1993 on fungicidal and insecticidal modes of action.)

**margosa oil, nim oil (= neem extract, PC Code 025006) [CAS No. 8002-65-1]**

A synonym for neem oil (= neem oil extract, PC Code 025006) expressed from seed-kernels of the Indian tree, *Azadirachta indica*, L. (Merck Index 11: 6357, MRID Nos. 426125-02, -03, -05, -06, -07)

**raw neem oil**

Interpreted as a synonym for a hydrophobic extract of neem oil (= neem extract, PC Code 025006) GRACE (151-13), MRID No. 426125-05)

3. **Formulated Products Containing CHEX Neem Oil (025007) (PC Code 025007)**

**NeemGuard™ Botanical Insecticide/Fungicide. Biochemical. (11688-O)**

A formulated product consisting of 90% CHEX Neem Oil (025007) and inerts for management of black spot, rusts, and powdery mildew on bedding plants, ornamentals, trees and shrubs and insects in and around greenhouses, commercial nurseries, and homes.

**NeemGard™ Botanical Insecticide. Biochemical. (11688-RI)**

A formulated product consisting of 90% CHEX Neem Oil (025007) and a surfactant for control of a variety of foliar plant diseases including rots, mildew, rusts, leaf spots, scab and blights. Kills/repels insect pests, such as whiteflies, aphids, scales, mealybugs, and mites.

4. **Other Formulated Products Derived from the Neem Tree [Partial Listing]**

**Margosan-O® (azadirachtin, PC Code 121701, neem extract, CAS No. 992-20-1)**

A neem formulation approved by EPA for limited use as a pesticide on non-food crops [Chem. & Eng. News 63: May 27, 1985; Merck Index 11: 6357].]

**SuperNeem™ 4.5-B Botanical Insecticide. 11688-13**

Azadirachtin (CAS 11141-17-6) in processed Neem Concentrate TGA1